DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 201

[Docket No. 90N–0309]

Drug Labeling; Sodium Labeling for Over-the-Counter Drugs; Technical Amendment; Termination of Delay of Effective Date; Compliance Dates

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule; technical amendment; termination of delay of effective date; compliance dates.

SUMMARY: The Food and Drug Administration (FDA) is amending the regulation that established conditions under which the labeling of over-the-counter (OTC) drug products intended for oral ingestion must include the sodium content and a general warning that persons who are on a sodium restricted diet should not take the product unless directed by a doctor. This final rule makes a few minor labeling changes and broadens the conditions for using the descriptive term "sodium free." This document also terminates the delay of the effective date of the provisions concerning sodium labeling (§ 201.64(a) through (h)) and establishes compliance dates for the final rule.

DATES: The effective date for § 201.64(a) through (h), added at 61 FR 17806, April 22, 1996, and delayed at 62 FR 19923, April 24, 1997, as amended by this final rule is [*insert date 30 days after date of publication in the* **Federal Register**]. The amendments in this final rule are effective [*insert date 30 days after date of publication in the* **Federal Register**].

Compliance Dates: The compliance date for any single entity and combination products subject to drug marketing applications approved on or after [*insert date 30 days after date of publication in the* **Federal Register**], is immediately upon approval of the application. The compliance date for all other OTC drug products, whether subject to drug marketing applications approved before [*insert date 30 days after date of publication in the* **Federal Register**], subject to any OTC drug monograph, or not yet the subject of any OTC drug monograph, is [*insert date 18 months after date of publication in the* **Federal Register**].

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SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of April 22, 1996 (61 FR 17798), FDA issued a final rule amending the general labeling provisions for OTC drug products (§ 201.64) to: (1) Require that the sodium content of all OTC drug products intended for oral ingestion be included in labeling when the product contains 5 milligrams (mg) or more sodium per a single dose; (2) require that all OTC drug products intended for oral ingestion containing more than 140 mg sodium in the labeled maximum daily dose bear a general warning that persons who are on a sodium-restricted diet should not take the product unless directed by a doctor; and (3) provide for the voluntary use of certain terms ("sodium free," "very low sodium," and "low sodium") relating to an OTC drug product's sodium content per labeled maximum daily dose. The effective date of the final rule was April 22, 1997. In the final rule, FDA also sought

comments whether the rule should be amended to include sodium content labeling for OTC rectal laxative, vaginal, dentifrice, mouthwash, and mouth rinse drug products.

Interested persons were invited to submit comments by July 22, 1996. In response to two requests for extension of time to file comments to the final rule, FDA published a document in the **Federal Register** of July 22, 1996 (61 FR 38046), extending the comment period until September 20, 1996.

In response to the final rule, FDA received comments from four manufacturers and two trade associations. Two of the comments requested that the effective date of the final rule be extended for at least an additional 6 months, to October 1997 or later. One comment mentioned the need for ongoing technical work, noting that manufacturers have undertaken formal product testing to ascertain precise sodium content before preparing new labels with accurate content declarations. The comment identified several problems with the sodium content of inactive ingredients. Specifications for some OTC drug ingredients do not include limits for sodium; suppliers often do not provide entire formulation information to companies; and sodium content may vary from lot to lot and/or supplier to supplier, especially for ingredients of natural origin. The comment stated that it would be difficult for some companies to complete product testing in time to have new labeling prepared by April 1997. The other comment stated that additional time would reduce label obsolescence, allow the use of already printed labeling, and allow labeling to be changed using current staff levels.

Both comments emphasized that FDA should delay implementation of the sodium labeling final rule until the proposed rule on labeling for OTC drug products containing calcium, magnesium, and potassium (61 FR 17807, April

22, 1996) was finalized. The comments contended that coordinating the effective date of both rules, which could apply to any single product, would avoid two label changes and the related economic impact of phasing in label changes for two separate rulemakings. One comment added that no major public health consequence should be expected from this delay for the sodium labeling because OTC drug products with relatively high sodium contents, e.g., antacids and laxatives, already bear a restricted sodium-use warning.

FDA agreed with the comments' rationale that it was desirable to coordinate implementation of the sodium labeling with the calcium, magnesium, and potassium labeling. A single effective date for both final rules avoids two labeling changes and reduces the economic impact of phasing in labeling changes for two separate, but related, rulemakings. In addition, a delay would provide manufacturers additional time that should be sufficient to complete all product analyses. FDA notified all commentors of its intentions in a feedback letter (Ref. 1) and asked the Consumer Healthcare Products Association (formerly the Nonprescription Drug Manufacturers Association) to notify its members and suggest that they incorporate calcium, magnesium, and potassium analyses into current plans to do sodium analyses so that all analyses can be completed and new labeling implemented by the effective date. FDA also concurred with one comment that there should be no major public health consequences because of this delay.

In the **Federal Register** of April 24, 1997 (62 FR 19923), FDA delayed the effective date of § 201.64(a) through (h) until further notice. The current final rule terminates the delay of the effective date, establishes a new effective date of 30 days after the date of publication in the **Federal Register**, and sets dates for manufacturers to be in compliance with the final rule.

Elsewhere in this issue of the **Federal Register**, FDA is publishing a final rule containing the labeling requirements for orally ingested OTC drug products containing calcium, magnesium, and potassium. That final rule also becomes effective 30 days after the date of publication in the **Federal Register**, and has the same compliance dates as this final rule for sodium labeling.

II. FDA's Response to the Comments

A. Situations Where Rule Should Not Apply

1. Two comments disagreed with across-the-board sodium labeling for all orally ingested OTC drug products. The comments favored a category-by-category approach for considering warnings and cited the review of OTC antacid and laxative drug products as examples that had successfully established the need for sodium warnings for those products. One comment added that FDA should not require sodium-related warnings on additional categories of OTC drug products without sufficient evidence of a public health need. The comment contended that people who have been advised by a physician or decided on their own to monitor their sodium intake are able to use content declarations to make food selections in their targeted limit and would be able to similarly use the content declaration on OTC drug products. The comment argued that the warning to avoid the product if on a sodium-restricted diet, unless directed by a doctor, is not needed and would not help consumers make decisions. The comment acknowledged, however, that information about the sodium content in a dosage unit is useful for people who are monitoring sodium intake.

A third comment contended that a warning statement is not necessary or helpful and is not a good use of limited OTC drug label space. The comment stated that people on a restricted diet are typically instructed by a medical

professional to be aware of certain habits and monitor their intake using information provided by the declared sodium level on a product. The comment added that the sodium content per dose declaration helps those people make choices in order to limit sodium intake and contended that the content labeling on a per dose basis alone is the most useful information for the consumer. The comment endorsed the proposed declaration of sodium content on OTC drug labels but opposed the warning statement. The comment concluded that the warning statement does not help people on a sodium-restricted diet make decisions, is unnecessary for the general population, tends to confuse consumers, and is inconsistent with FDA's position that warning statements be clinically significant and important for the safe and effective use of a product by consumers.

FDA appreciates the one comment's endorsement of the sodium content declaration part of the regulation, but disagrees with the comments' arguments that the warning statement is unnecessary and should not apply to all orally ingested OTC drug products.

FDA addressed this issue in comment 4 of the sodium labeling final rule (61 FR 17798 at 17799 to 17800). FDA stated that across-the-board labeling has been used during the OTC drug review, instead of category-by-category, when the situation warrants, such as the pregnancy-nursing warning for OTC drug products in § 201.63 (21 CFR 201.63). FDA indicated that there was sufficient evidence of a public health need for this warning because a certain level (140 mg) of sodium may present a potential safety problem, regardless of the source of the sodium, and an across-the-board approach was based on sodium being present in any OTC drug product. FDA also believes that the warning is necessary for the entire population. Currently, there is no reliable

genetic marker to determine susceptibility to sodium-induced hypertension. Because salt sensitive persons cannot be identified, FDA believes that it is prudent to recommend caution concerning sodium intake for the general population. Therefore, FDA deemed a category-by-category or limited approach inappropriate.

FDA also pointed out that implementation of a warning on a category-by-category basis would result in a lack of uniformity in OTC drug product labeling until FDA's evaluation of each drug category was completed. FDA notes that one of the comments also stated that the sodium labeling final rule affects thousands of OTC drug products. FDA finds that another important reason why sodium labeling requirements should be implemented across-the-board and become effective at the same time.

FDA notes that a number of the comments submitted in response to the April 25, 1991 (56 FR 19222), proposal to require sodium labeling stated that this labeling would be especially helpful to those individuals who must restrict their sodium intake, especially the elderly. (See comment 1 at 61 FR 17798.) FDA strongly believes that the addition of sodium content (per dosage unit) information in OTC drug product labeling will assist consumers in selecting the desirable and appropriate product. However, FDA has determined that this information alone may not provide consumers complete and adequate guidance. FDA firmly believes that consumers on a sodium-restricted diet should be informed to check with their doctor not to use a particular product if it contains above a certain level of sodium in the labeled maximum daily dose of the product. A warning of this type has been required on OTC antacid drug products for almost 30 years, and there is no evidence that it has confused consumers. FDA concludes that this warning statement will help consumers

make better-informed decisions and will result in safer use of OTC drug products containing sodium by those consumers who must or wish to monitor their sodium intake.

2. One comment noted that liquid and chewable products, many of which are intended for use in children because of difficulty or reluctance to swallow a whole tablet, are likely to have a higher sodium content. The sodium comes from inactive ingredients such as flavors and sweeteners (e.g., sodium saccharin) used to make the products more palatable. The comment stated that it would be unfortunate if a child was not given a product because of the sodium content labeling. The comment added that the advantages of using the more suitable dosage forms of children's products outweighed any risk from ingestion of small amounts of sodium. The comment contended that children are not likely to require such a restriction and that the sodium declaration on children's products is unnecessary information that is likely to confuse consumers because the information is meant for people who are not likely to use the product. The comment asked FDA to reconsider the necessity for sodium labeling on OTC drug products directed for intermittent use in children.

FDA has reconsidered the sodium labeling requirements for liquid and chewable products, including those directed for use in children, and determined that the labeling serves several useful functions. First, some children need to limit sodium intake for medical reasons. Second, and more important, a number of adults, especially the elderly, prefer liquid and chewable dosage forms because of swallowing problems or reluctance to swallow a whole tablet or capsule. Sodium labeling information is especially

important for elderly people who may have to limit their sodium intake for medical reasons.

FDA concludes that sodium labeling information on liquid and chewable tablet products will be useful to consumers who need or desire this information and will not be confusing to those consumers who have no need for the information. FDA believes the same reasoning applies to inactive ingredient information. This information is not of interest to every consumer, but is important for those consumers who need or want it. According to a 1988 Diet and Health Survey (Ref. 2), sodium remains the most commonly mentioned component that consumers try to avoid in their diet. Moreover, another survey (Ref. 3) reported that 88 percent of shoppers felt label information on sodium was either very or somewhat important. FDA has not received any reports that this information is confusing to consumers who have no interest in it.

3. Five comments responded to FDA's request about expanding the sodium content labeling to OTC rectal laxative, vaginal, dentifrice, mouthwash, and mouth rinse drug products. All felt strongly that such labeling would be inappropriate and unnecessary for these products. The comments pointed out that dentifrices, mouthwashes, and mouth rinses are intended to be spit out and not swallowed. The comments mentioned that if a consumer swallowed a small amount of the product the amount of sodium ingested would be minuscule. Two comments added that the amount of sodium absorbed from the oral mucosa during approximately 30 seconds to 1 minute of use would be insignificant. The comments contended that quantification of any amount of potentially absorbed sodium from dentifrices, mouthwashes, and mouth rinses would be difficult and meaningless because these products are used and

spit out in varying quantities. The comments concluded that sodium content labeling would not provide consumers who use these products any useful information. Two comments added that FDA had reached the same conclusion when it changed the scope of the sodium labeling regulation from "orally administered OTC drug products" to "OTC drug products intended for oral ingestion."

Two comments stated that products intended for vaginal or rectal administration should not be labeled for sodium content. The comments contended that consumers would likely be confused by this labeling, which is viewed as nutritional content labeling, and would not know how to use the information. The comments added that such labeling might cause consumers to mistakenly assume such products are meant for ingestion and thus orally use suppositories or liquid meant for vaginal or rectal use.

FDA generally concurs with the comments and, at this time, is not requiring sodium labeling for OTC vaginal, dentifrice, mouthwash, or mouth rinse drug products. Because of reports of problems associated with rectal enemas containing sodium phosphate/sodium biphosphate (where the product has not produced a bowel movement and has been retained in the body), FDA is proposing sodium content labeling for these products. These products contain a high sodium content and may represent a problem to people who need to limit sodium intake. Elsewhere in this issue of the **Federal Register**, FDA is proposing to amend § 201.64 to include sodium content labeling for OTC rectal drug products containing sodium phosphate/sodium biphosphate.

B. Dose That Triggers Sodium Content Declaration

4. One comment requested that § 201.64(a) be amended to state the specific recommended dose, which presumably is the maximum recommended dose,

that triggers the requirement to declare the sodium content on the product label. The comment contended that some of the preamble to the final rule appears to be inconsistent with § 201.64(a), which states that the criterion for a required declaration of sodium content is 5 mg or more sodium in a "single recommended dose of the product (which may be one or more dosage units)." The comment felt that the statement that "The agency * * * decided to use 5 mg of sodium per maximum recommended dose as the basis for including sodium content in the labeling of OTC drug products" (61 FR 17798 at 17800) was inconsistent with § 201.64(a).

FDA addressed this issue in comment 8 of the preamble to the final rule (61 FR 17798 at 17800). We acknowledge that the discussion might have been confusing in some regards. FDA stated that a 5 mg maximum labeled dose is consistent with the antacid monograph, which has been in effect since 1974. FDA noted that the requirement for OTC antacid drug products in § 331.30(f) (21 CFR 331.30(f)), which was removed in the sodium labeling final rule, provides that the labeling include sodium content per dosage unit if it contains 5 mg or more. Because the sodium content declaration can vary from product to product if based on the maximum daily dose of the product, FDA deemed it important to have a fixed number at which the sodium content per dosage unit would have to be declared. FDA determined that the amount per single recommended dose was the most useful information to consumers.

The criterion in § 201.64(a) determines whether there is a need for a sodium content declaration. The intent of the final rule was to require content declaration based on the amount of sodium present in the maximum number of dosage units recommended for a single dose. Thus, if one tablet contains 4 mg of sodium and the recommended dosage range is "one or two" tablets,

sodium content labeling (in mg per dosage unit) would be required because two tablets exceed the 5 mg threshold. Because a single recommended dose may include one or more dosage units, FDA believes the term "single maximum recommended dose" is a better term than "single recommended dose" to state the basis for requiring sodium content labeling. Accordingly, FDA is amending § 201.64(a).

C. Placement of the Sodium Content Declaration

5. One comment requested that FDA allow flexibility in the placement of the sodium content declaration so that it would not have to be on a separate line, as required by § 201.64 (b). The comment requested that the information be allowed to be part of a paragraph listing of ingredients that would include other cations, e.g., calcium, magnesium, and potassium, per the FDA proposed rule for orally ingested OTC drug products containing those ingredients (61 FR 17807, April 22, 1996). The comment stated that such a paragraph listing could include as many content declarations as required and appear as follows: "Each tablet contains: sodium (_____ mg), calcium (_____ mg), magnesium (_____ mg), potassium (_____ mg)." The comment contended that such flexibility was especially important for small packages where economy of space is important and placement of sodium content on a separate line would be difficult.

The comment also requested as another alternative that other means, such as color, boldface, underlining, etc., be allowed to give prominence to a new type of information within the listing of ingredients so that the sodium content declaration is readily visible within the paragraph listing of inactive ingredients. In addition, the comment requested clarification whether the

sodium declaration is supposed to follow the required listing of active ingredients or the voluntary listing of inactive ingredients.

Since the sodium labeling final rule was published on April 22, 1996, FDA has addressed this issue in a final rule on a general labeling format for all OTC drug products (64 FR 13254, March 17, 1999). That final rule established a specific order and format in which information must appear in OTC drug product labeling. Section 201.66(c)(7)(i) (21 CFR 201.66(c)(7)(i)) states that required information about certain ingredients in OTC drug products (e.g., sodium in § 201.64(b)) shall appear as follows: "each (insert appropriate dosage unit) contains:" [in bold type] (insert name(s) of ingredient(s) and the quantity of each ingredient). This information shall be the first statement under the heading "Other information." Concurrently, FDA revised the last sentence in § 201.64(b) to state: "The sodium content per dosage unit shall follow the heading "Other information" as stated in § 201.66(c)(7)." (See 64 FR 13254 at 13286.) Elsewhere in this issue of the **Federal Register**, FDA is revising § 201.66(c)(7)(i) to include calcium, magnesium, and potassium and their CFR citations as other examples covered by that section.

D. Rounding-off to the Nearest 5 Mg

6. Three comments disagreed with the sodium content having to be rounded-off to the nearest whole number. The comments argued that this requirement was inconsistent with the food labeling regulations, which allow rounding to the nearest 5-mg level rather than to the nearest whole number (1-mg level). One comment contended that allowing for the 5-mg increment in sodium labeling for OTC drug products would reduce the cost of label changes for lot-to-lot variations in sodium content and would protect consumers from industry label conversion costs associated with minor

reformulations that result in minor sodium content changes. The comment stated that FDA had presented no basis for requiring drug products to contain more accurate sodium content labeling than food products. Another comment mentioned the potential variability in the sodium content of ingredients of natural origin, as occurs with food products. The comment was concerned that the additive effect of sodium as an unassayed component in multiple raw materials could result in an OTC drug product containing greater than 5 mg sodium per dosage unit and thus result in inaccurate labeling. For this reason, the comment contended that manufacturers should be permitted to round the sodium content declaration to the nearest 5-mg level, as permitted in food product labeling.

FDA discussed this issue in response to a comment's concern in comment 3 of the preamble of the final rule for sodium labeling (61 FR 17798 at 17799). The author of the comment was concerned that descriptive terms based on sodium content using rounded-off numbers could be different from descriptive terms based on sodium content using actual numbers.

FDA discussed how rounding-off could result in potential discrepancies between the actual and apparent sodium content in OTC drug products, and may lead to consumer confusion. For instance, if the actual sodium content of a product is 8 mg per dosage unit and the product is to be taken four times daily, the labeled maximum daily dose is 32 mg. Because the sodium content is less than 35 mg (per labeled maximum daily dose), the term "very low sodium" could be used. However, if the actual dosage unit (8 mg) is rounded-off to 10 mg, the apparent labeled maximum daily dose for that product would be 40 mg and the descriptive term would be "low sodium". FDA did note that regulations for labeling food provide for the rounding-off to the nearest

5 to 10 mg sodium per serving. We explained that a larger rounding-off range is more appropriate in the context of food because most food products contain naturally occurring sodium and variation in sodium content is expected. On the other hand, most OTC drug products are manufactured and the amount of sodium in products can be strictly controlled. Thus, the sodium content of OTC drug products is expected to be less variable than that of foods and can be more accurately described on the label. Based on this discussion, FDA concluded that the 5-mg rounding rule for foods should not be used in the OTC drug content even if it results in different criteria for food and drug products.

FDA has considered the current comments' concerns, but is not persuaded to change its position. Based on the example discussed herein, minor reformulation of a drug product may result in a change in descriptive category when using the 5-mg rounding rule for foods, but no change if the foods rule is not applied. For example, if the sodium content of a drug product that is taken four times a day increases from 7 mg [5 mg under the 5-mg rounding rule] to 8 mg [10 mg under the same rule] per dosage unit, that increase would change the descriptive category from "very low sodium" (20 mg per labeled maximum daily dose) to "low sodium" (40 mg per labeled maximum daily dose). However, when the 5-mg rounding rule is not applied, the descriptive category ("very low sodium") is the same before and after reformulation (28 and 32 mg, respectively).

Further, FDA notes that the amount of sodium (140 mg) present in a product to require the warning in § 201.64 (c) is much lower than the amount of calcium (3.2 g), magnesium (600 mg), or potassium (975 mg) that trigger a similar warning for these cations. Therefore, rounding-off to the nearest 1

mg provides consumers more accurate information about sodium content in OTC drug products.

FDA believes that because the sodium content in drug products is less variable than for foods, and can be determined more accurately, consumers should have the more accurate information. Thus, providing consumers attempting to monitor their sodium intake with more accurate information, to use in their ingredient calculations, should increase consumer safety. FDA continues to believe that rounding-off to the nearest whole number will result in less consumer confusion and add to consumer safety, and that any associated industry label conversion costs associated with minor reformulations that may result in minor sodium content changes will be minimal. The comment provided no information to indicate what these conversion costs might be or that they would have any impact on consumers. Analysis of product lots for variations in sodium content is discussed in section II.G, comment 11 of this document.

E. Sodium Versus Sodium Chloride Content

7. One comment disagreed with FDA's conclusion that sodium content labeling should reflect sodium content without regard to the anion (e.g., chloride) with which the sodium is associated in the drug product formulation. The comment referred to its previous comments on this issue, which FDA addressed in comment 16 of the preamble of the final rule for sodium labeling (61 FR 17798 at 17803 to 17804). Referring to that response, the comment noted that FDA had stated that hypertension was not the sole reason for adoption of sodium labeling requirements and that the only other example that FDA mentioned was that sodium bicarbonate had been reported to exacerbate congestive heart failure. The comment added that it had reviewed the

rulemakings for other sodium labeling proceedings and they showed that hypertension has been, if not the only, certainly the principal rationale supporting sodium content labeling and warning requirements. The comment indicated that the scientific literature did not support the very low levels of sodium present in OTC drug products as being of significant concern in the management of congestive heart failure. The comment concluded that the final rule should have required salt (sodium chloride) content labeling and not just sodium content labeling.

FDA can appreciate the comment's views, but does not agree with them. FDA recognized in comment 16 of the preamble of the final rule for sodium labeling that there were differences of opinion on the relationship of sodium and hypertension. FDA provided an extensive discussion on this issue there and sees no reason to repeat it here. FDA also pointed out that sodium labeling is not aimed specifically at persons with hypertension, but is intended to benefit all people who need or wish to monitor their sodium intake for whatever reason. Accordingly, FDA is not changing the sodium labeling requirement from "sodium" content to "sodium chloride (salt)" content.

F. Descriptive Terms

8. Two comments contended that the descriptive terms "sodium free," "very low sodium," and "low sodium" should be based on the amount of sodium in a single dose rather than on the total content in the labeled maximum daily dose. The comments noted that these descriptive terms for food labeling are based on the content in one serving. One comment added that labeling OTC drug products on the basis of dosage unit is more consistent with the food labeling system, in which content labeling and voluntary descriptive terms are based on a "serving." The other comment added that

consumers often use only one dose of an OTC drug product and, because of the inconsistency with the food labeling regulations, it is more relevant and consistent to describe the sodium content of OTC drug products on a per dose basis.

FDA disagrees with the comments. Many OTC drugs that contain sodium have daily dosing that involves more than one dose. Basing the descriptive terms on a single dose would potentially be misleading to consumers because it is the maximum daily dose of the product that determines the consumer's daily sodium intake from the OTC drug product.

9. Two comments requested that FDA change the requirement for use of the term "sodium free." One comment stated that, as a practical matter, it would seem reasonable to allow a product containing less than 0.5 mg of sodium per dosage unit to be called "sodium free," even though the amount was not zero, if the labeled maximum daily dose contains less than 5 mg of sodium. The comment stated that the addition of this amount of sodium to a consumer's sodium load is comparably negligible from a clinical standpoint. The comment noted FDA's statement in the preamble to the sodium labeling final rule (61 FR 17798 at 17800) that "the agency considers a sodium level below 5 mg per dose to be physiologically insignificant."

The other comment pointed out that it marketed a product with a sodium content between 0.1 to 0.2 mg per tablet and less than 5 mg in the maximum labeled daily dose. The commentcomplained that the final rule would prevent this product from being labeled as "sodium free," when it has been labeled as "sodium free" for over 10 years. The comment contended that the final rule allowing "sodium free" to be used only when the maximum daily dose contains less than 0.5 mg sodium is more stringent than necessary for

consumer protection and avoiding consumer confusion. The comment stated that the final rule as written would effectively eliminate the use of the term "sodium free" from OTC drug product labeling. The comment suggested that § 201.64(d) be revised to read: The term "sodium free" may be used in the labeling of OTC drug products intended for oral ingestion if the amount of sodium in the labeled maximum daily dose is less than 5 milligrams and the amount of sodium per dosage unit is 0 milligram (when rounded-off as per paragraph (b) of this section).

The comment noted that its proposed revision, like the final rule, eliminates the possibility that products labeled "sodium free" will at the same time be labeled with a sodium content greater than "0 mg," which would be a potential basis for consumer confusion. The comment concluded that consumers would be better served by the suggested revision of the final rule, and that the minor change also accomplishes FDA's objectives.

FDA agrees with the comments. Accordingly, in this technical amendment, FDA is revising § 201.64(d) to read: "The term "sodium free" may be used * * * if the amount of sodium in the labeled maximum daily dose is 5 milligrams or less and the amount of sodium per dosage unit is 0 milligram (when rounded-off in accord with paragraph (b) of this section)."

G. Economic Impact

10. One comment stated that the economic impact of the final rule is substantially greater than presumed by FDA, based on information that companies provided. The comment stated that the sodium labeling requirement could potentially add costs for manufacturers, and therefore for consumers, when labels must be changed even if a minor reformulation results in a relatively minor change in the amount of sodium in a finished OTC drug

product. The comment added that companies were still assessing the actual economic impact related to product analysis for sodium, calcium, magnesium, and potassium, and would submit additional information when it becomes available.

Another comment stated that it was uncertain of the full impact of the final rule. It estimated that the rule has the potential to impact an estimated 1,500 stockkeeping units (SKUs), which could result in a $1 million impact for art and obsolescence costs alone.

FDA notes that, unfortunately, industry did not provide any comments on the agency's economic impact determination that appeared in the proposed rule for sodium labeling (56 FR 19222 at 19225). At that time (April 25, 1991), FDA estimated the relabeling cost for manufacturers who marketed products containing sodium to be less than $500,000 for the entire industry. That estimate was based on the number of products that would be affected by the final rule, the number of distinct label changes, and the cost of printing new labels. The estimate did not include any projections for product analyses because that issue had not been raised in the rulemaking. FDA did state in the final rule for sodium labeling (61 FR 17798 at 17799) that most OTC drug products are manufactured and the amount of sodium in products can be strictly controlled. The industry has indicated that it would provide additional information on the cost of product analyses when available, but has not done so to date. The current final rule provides for coordination of the sodium labeling requirements with the implementation of the rule requiring calcium, magnesium, and potassium labeling, published elsewhere in this issue of the **Federal Register**. This coordination should reduce the economic impact for products containing sodium and one or more of the other cations.

11. One comment asked whether FDA expected cation analysis for every manufactured lot of OTC drug products and, if yes, whether the labeling had to bear the exact amount of assayed cation. The comment stated that if this were required to be done, this would mean that labeling needed to be printed for each lot, which would have a significant economic implication. The comment asked whether a company can base cation content on average values (taken from historical lots) and known lot-to-lot variations, and what amount of variation would be acceptable without a need for a change in the sodium content declaration.

FDA's position is that manufacturers must use the same standards for labeling of sodium (or other cations) as used to assure accurate content labeling of active ingredients in OTC drug products. Manufacturers are expected to follow good manufacturing practices (21 CFR part 211) and general guidance provided by the United States Pharmacopeia/National Formulary in determining a product's cation content.

FDA recognizes that there is some acceptable variation between different product lots that bear the same labeling. The amount of an ingredient declared in the labeling is a composite value derived from a number of product samples. Some content determinations for some lots may be based, in part, on average values (taken from historical lots) and on known lot-to-lot variations. However, manufacturers should be able to ascertain when it is necessary to do new analyses, e.g., when a raw material is purchased from a new supplier or the raw material contains a sodium declaration that differs from previous lots. Many compendial monographs provide that a product contains not less than 90 percent and not more than 110 percent of the labeled amount of an active ingredient. FDA considers this ±10 percent criterion as acceptable for cation

content labeling. FDA does not see a need for cation content information from individual batch analysis to appear in product labeling. However, when batch analyses reflect greater than ±10 percent in cation content, relabeling should occur. Therefore, there should not be a significant economic implication for manufacturers.

III. Summary of Significant Changes

1. This final rule terminates the delay of the effective date of paragraphs (a) through (h) of § 201.64 and establishes compliance dates for sodium labeling of OTC drug products. (See the **DATES** section and section I of this document.)

2. FDA is revising § 201.66(a) to more clearly state the basis for requiring sodium content labeling. (See section II.B, comment 4 of this document.)

3. The sodium content per dosage unit follows the heading "Other information" as stated in § 201.66(c)(7). (See section II.C, comment 5 of this document.)

4. FDA is revising § 201.64(c) to state the sodium-restricted diet warning in the new OTC drug product labeling format.

5. FDA is revising § 201.64(d) to expand the conditions for use of the term "sodium free" for products containing 5 mg or less of sodium in the labeled maximum daily dose. This technical amendment allows for the use of the term "sodium free" when the amount of sodium per dosage unit is 0 mg (when rounded-off in accord with § 201.64(b)) and the labeled maximum daily dose contains 5 mg or less sodium. (See section II.F, comment 9 of this document.)

IV. FDA's Final Conclusions on Sodium Labeling

A. New Labeling Requirements

FDA concludes that public interest and public health consequences related to sodium intake have produced a need for more informative and consistent sodium content and warning information in the labeling of OTC drug products. This is especially true for individuals with hypertension, heart failure, or other conditions who must monitor their sodium intake.

FDA is implementing the following content and warning requirements for OTC drug products intended for oral ingestion: Content—if the product contains 5 mg sodium or more per single maximum recommended dose; warning—if the product contains more than 140 mg sodium in the labeled maximum daily dose. The content labeling shall be rounded-off to the nearest whole number and shall appear after the heading "Other information." The sodium labeling requirements apply to OTC drug products intended for oral ingestion, whether marketed under an OTC drug monograph, the ongoing OTC drug review, an approved application, or no application. This final rule terminates the delay of the effective date of paragraphs (a) through (h) of § 201.64 and establishes compliance dates for sodium labeling of OTC drug products.

B. Statement About Warnings

Mandating warnings in an OTC drug product regulation does not require a finding that any or all of the OTC drug products covered by the regulation actually caused an adverse event, and FDA does not so find. Nor does FDA's requirement of warnings repudiate the prior OTC drug monographs and regulations under which the affected drug products have been lawfully marketed. Rather, as a consumer protection agency, FDA has determined that

warnings are necessary to ensure that these OTC drug products continue to be safe and effective for their labeled indications under ordinary conditions of use as those terms are defined in the Federal Food, Drug, and Cosmetic Act (the act). This judgment balances the benefits of these drug products against their potential risks (see 21 CFR 330.10(a)).

FDA's decision to act in this instance need not meet the standard of proof required to prevail in a private tort action (*Glastetter* v. *Novartis Pharmaceuticals Corp.*, 252 F.3d 986, 991 (8th Cir. 2001)). To mandate warnings, or take similar regulatory action, FDA need not show, nor do we allege, actual causation. For an expanded discussion of case law supporting FDA's authority to require such warnings, see the final rule entitled "Labeling of Diphenhydramine-Containing Drug Products for Over-the-Counter Human Use" (67 FR 72555, December 6, 2002).

C. Statutory Authority

In this final rule, FDA is addressing legal issues relating to the agency's action to require sodium content labeling for OTC drug products. FDA is relying on section 502(e) of the act (21 U.S.C. 352(e)) to require disclosure in the labeling of OTC drug products of: (1) The presence and quantity of sodium that is an active ingredient, and (2) the presence of sodium that is an inactive ingredient. To require disclosure of the quantity of sodium that is an inactive ingredient, FDA is relying on sections 502(a) and 201(n) of the act (21 U.S.C. 321(n)).

Section 502(e) of the act deems a drug to be misbranded unless its label bears the established name and quantity of each active ingredient or, if determined to be appropriate by the Secretary of Health and Human Services (the Secretary), the proportion of each active ingredient (21 U.S.C.

352(e)(1)(A)(ii)). That provision also deems a drug to be misbranded unless its label bears the established name of each inactive ingredient on the outside container, and if determined appropriate by the Secretary, on the immediate container (21 U.S.C. 352(e)(1)(A)(iii)). Under section 502(a) of the act, a drug is deemed to be misbranded if its labeling is "false or misleading in any particular." Section 201(n) of the act amplifies what is meant by "misleading" in section 502(a). Section 201(n) states that, in determining whether labeling is misleading, FDA shall take into account not only representations made about the product, but also the extent to which the labeling fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling relates under the conditions of use prescribed in the labeling, or under such conditions of use as are customary or usual (see § 1.21 (21 CFR 1.21)). Finally, FDA has authority under section 701(a) of the act (21 U.S.C. 371(a)) to issue regulations for the efficient enforcement of the act.

As discussed in sections I, II, and IV of this document and in the final rule (61 FR 17798), FDA has determined that for OTC drug products containing more than the specified amount of sodium, the quantity of this substance as an inactive ingredient in OTC drug products is material with respect to consequences that may result from use of such products within the meaning of section 201(n) of the act. Certain levels of sodium present a potential safety problem. People with hypertension, heart failure, or other conditions need to monitor their intake of sodium, which can cause serious toxicity in persons with these conditions. Many people are on sodium-restricted diets. Other people must monitor their intake of sodium from foods (including dietary supplements) and OTC drugs for other medical or health reasons. Absent

mandatory sodium content labeling, these people would not be able to understand the relative contribution that OTC drug products make to their intake of sodium, and would not be able to compare the sodium content of various OTC drug products.

D. The First Amendment

This final rule passes muster under the first amendment. FDA's requirement of sodium content labeling for OTC drug products (where sodium is an inactive ingredient and is present beyond the specified threshold level) is constitutionally permissible because it is reasonably related to the government's interest in preventing deception of consumers and because it is not an "unjustified or unduly burdensome" disclosure requirement that offends the first amendment. (See *Zauderer* v. *Office of Disciplinary Counsel*, 471 U.S. 626, 651 (1985); see also *Ibanez* v. *Florida Dep't of Bus. and Prof'l Regulation*, 512 U.S. 136, 146 (1994)). Such a reasonable relationship is plain here. The prescribed labeling disclosure would contribute directly to the consumption of quantities of sodium that do not threaten the health of people for whom sodium use has material consequences. Some people, newly informed by the required labeling, will properly reduce or discontinue their intake of sodium-containing OTC drug products and thereby protect and promote their own health. By encouraging such changes in behavior, the labeling requirement is rationally related to the government's goal of ensuring appropriate sodium consumption. Finally, it is not "unduly burdensome" to require an additional disclosure of this kind.

In any event, this final rule passes muster when analyzed under the four-part test in *Central Hudson Gas and Electric Corporation* v. *Public Service Commission*, 447 U.S. 557 (1980), because it is necessary for the labeling of

OTC drug products containing sodium in excess of the threshold amount to be nonmisleading (id. at 563–564). As discussed in this document, FDA has determined that the failure to disclose in an OTC drug product's labeling the amount of sodium in the product when it is present in amounts exceeding a certain threshold misbrands the product because the failure causes the labeling to be false or misleading under sections 502(a) and 201(n) of the act.

Although this determination obviates the need for FDA to address the other three parts of the Central Hudson test, we believe that the sodium content labeling requirement satisfies each of these parts. With respect to the second part, FDA's interest in requiring sodium content labeling under this final rule is to ensure that people who must monitor their sodium intake for health reasons have information necessary to understand the relative contribution that OTC drug products make to their sodium intake and to compare the sodium content of OTC drug products. FDA's interest in protecting the public health has been previously upheld as a substantial government interest under *Central Hudson*. (See *Pearson* v. *Shalala*, 164 F.3d 650, 656 (D.C. Cir. 1999) (citing *Rubin* v. *Coors Brewing Co.*, 514 U.S. 476, 484–485 (1995)). The labeling requirement directly advances this interest, thereby satisfying the third part of the Central Hudson test, because by requiring labeling disclosure of the presence and quantity of sodium in OTC drug products, the rule gives people the precise information they need to determine whether a particular product is consistent with their health requirements.

Finally, under the fourth part of the Central Hudson test, there are not numerous and obvious (*Cincinnati* v. *Discovery Network*, 507 U.S. 410, 418 n. 13 (1993)) alternatives to mandatory sodium content labeling of OTC drug products that directly advance the government's interest but are less

burdensome to speech. Consumers are accustomed to using the label as their primary source of information about a product's contents. Neither a public education campaign, nor encouraging OTC drug product marketers to provide information on sodium content in the labeling of their products, would ensure that people have the information they need about sodium content at the point of sale or ingestion. And establishing limits on sodium content would be more harmful to the public health. It is unnecessary for consumers who are not at risk to reduce or closely monitor their added daily sodium intake from OTC drug products. Further, some consumers may wish to use OTC drug products to enrich the amount of sodium in their diets. Finally, for many products, the sodium content is linked to product design and determined by pharmaceutical necessity. Requiring disclosure here meets the fourth part of the test.

In conclusion, FDA believes it has complied with its burdens under the first amendment to support mandatory disclosure of the amount of sodium above a specified level in OTC drug product labeling.

V. Analysis of Impacts

FDA discussed the impacts of this sodium labeling requirement in the final rule for sodium labeling (61 FR 17798 at 17805 to 17806) and noted that no comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking. Since that time, FDA has received two comments. (See section II.G, comments 10 and 11 of this document.)

FDA has examined the impacts of this final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory

alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule has a significant economic impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement of anticipated costs and benefits before proposing any rule that may result in an expenditure in any one year by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million (adjusted annually for inflation).

FDA concludes that this final rule is consistent with the principles set out in Executive Order 12866 and in these two statutes. As discussed in this section, the final rule will not be economically significant as defined by the Executive order. With respect to the Regulatory Flexibility Act, FDA does not believe the rule would have a significant economic impact on a substantial number of small entities. The Unfunded Mandates Reform Act of 1995 does not require FDA to prepare a statement of costs and benefits for the final rule, because the final rule in not expected to result in any 1-year expenditure that would exceed $100 million adjusted for inflation. The current inflation adjusted statutory threshold is about $110 million.

The purpose of this final rule is to provide two minor labeling revisions, terminate the delay in the effective date, and set compliance dates for the final rule. The labeling revisions will not have any further economic impact. The termination of the delay in the effective date and the establishment of compliance dates will not have any additional economic impact above that

stated in the preamble to the final rule (61 FR 17798). Accordingly, FDA has not reconsidered its earlier certification that the final rule will not have a significant economic impact on a substantial number of small entities. For the reasons stated in this section and under the Regulatory Flexibility Act (5 U.S.C. 605(b)), FDA certifies that this rule will not have a significant economic impact on a substantial number of small entities.

VI. Paperwork Reduction Act of 1995

FDA concludes that the labeling requirements in this document are not subject to review by the Office of Management and Budget because they do not constitute a "collection of information" under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*). Rather, the labeling is a "public disclosure of information originally supplied by the Federal government to the recipient for the purpose of disclosure to the public" (5 CFR 1320.3(c)(2)).

VII. Environmental Impact

FDA has determined under 21 CFR 25.31(a) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VIII. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive

order and, consequently, a federalism summary impact statement is not required.

IX. References

The following references are on display in the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

(1) Letter from D. Bowen, FDA, to L. Totman, NDMA, January 14, 1999, coded LET 3.

(2) Levy, A. S. and J. T. Heimbach, Division of Consumer Studies, FDA, "Recent Public Education Efforts About Health and Diet in the United States," 200 C. St. SW., Washington, DC 20204, 1989.

(3) National Food Processors Association, "Summary of Findings, Food Labeling and Nutrition * * * What Americans Want," Washington, DC, 1990.

List of Subjects in 21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 201 is amended as follows:

PART 201—LABELING

■ 1. The authority citation for 21 CFR part 201 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 358, 360, 360b, 360gg–360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

■ 2. Section 201.64 is amended by revising paragraphs (a), (c), and (d) and by adding paragraph (j) to read as follows:

§ 201.64 Sodium labeling.

(a) The labeling of over-the-counter (OTC) drug products intended for oral ingestion shall contain the sodium content per dosage unit (e.g., tablet, teaspoonful) if the sodium content of a single maximum recommended dose of the product (which may be one or more dosage units) is 5 milligrams or more. OTC drug products intended for oral ingestion include gum and lozenge dosage forms, but do not include dentifrices, mouthwashes, or mouth rinses.

* * * * *

(c) The labeling of OTC drug products intended for oral ingestion shall contain the following statement under the heading "Warning" (or "Warnings" if it appears with additional warning statements) if the amount of sodium present in the labeled maximum daily dose of the product is more than 140 milligrams: "Ask a doctor before use if you have [in bold type] [bullet][1] a sodium-restricted diet". The warnings in §§ 201.64(c), 201.70(c), 201.71(c), and 201.72(c) may be combined, if applicable, provided the ingredients are listed in alphabetical order, e g., a calcium or sodium restricted diet.

(d) The term *sodium free* may be used in the labeling of OTC drug products intended for oral ingestion if the amount of sodium in the labeled maximum daily dose is 5 milligrams or less and the amount of sodium per dosage unit is 0 milligram (when rounded-off in accord with paragraph (b) of this section).

* * * * *

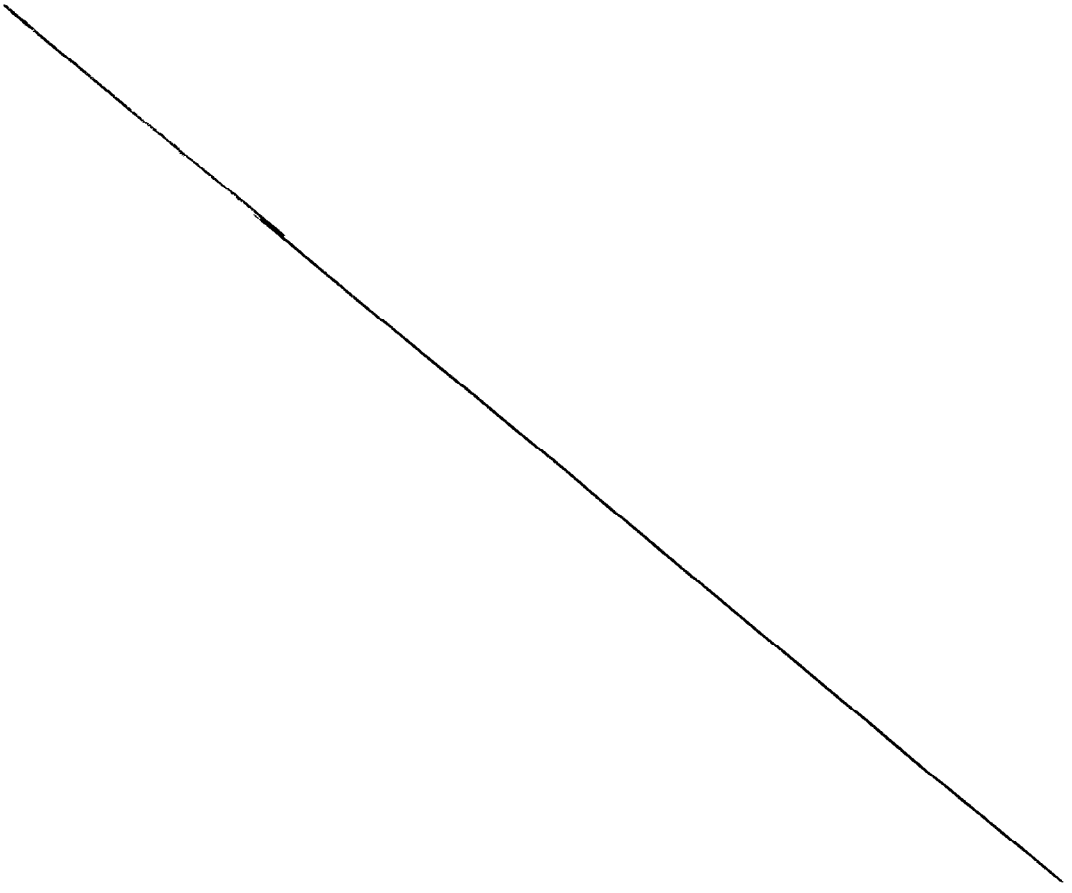
(j) Any product subject to paragraphs (a) through (h) of this section that is not labeled as required and that is initially introduced or initially delivered for introduction into interstate commerce after the following dates is

[1] See § 201 .66(b)(4) of this chapter for definition of bullet symbol.

misbranded under sections 201(n) and 502(a) and (f) of the Federal Food, Drug, and Cosmetic Act.

(1) As of the date of approval of the application for any single entity and combination products subject to drug marketing applications approved on or after [*insert date 30 days after date of publication in the* **Federal Register**].

(2) [*Insert date 18 months after date of publication in the* **Federal Register**], for all OTC drug products subject to any OTC drug monograph, not yet the subject of any OTC drug monograph, or subject to drug marketing applications approved before [*insert date 30 days after date of publication in the* **Federal Register**].



Dated: 3/16/04
March 15, 2004.

Jeffrey Shuren,
Assistant Commissioner for Policy.

[FR Doc. 04–????? Filed ??–??–04; 8:45 am]

BILLING CODE 4160–01–S